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(54) Title: PREPARATION FOR STRENGTHENING THE IMMUNE RESPONSE IN THE WALDEYER'S RING AND THE ORONASAL MUCOSA BY INTRANASAL ADMINISTRATION

(57) Abstract: A product to be administered by nose for preventing inflammatory or hypertrophic forms and strengthening the immune action in the Waldeyer's ring and the oronasal mucosa consists of a physiological action with a high concentration in a polysaccharide such as glucan. In particular, two solutions having different concentrations have been specified, namely a first physiological solution with a glucan concentration equal to 0.25 % for cleaning the nasal fossae and with a preventive hydrating, reepithelializing capability of strengthening the immune action in the Waldeyer's ring and the oronasal mucosa, and a physiological solution with a glucan concentration equal to 2 % for hydrating and reepithelializing the nasal mucosa, capable of strengthening the immune response in the Waldeyer's ring during the acute phase of the inflammatory, hypertrophic forms of the same. Glucan is preferably used in the form β -(1-3)-glucan.

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Preparation for strengthening the immune response in the Waldeyer's ring and the oronasal mucosa by intranasal administration

The present invention relates to a product to be administered by nose for preventing inflammatory or hypertrophic forms and strengthening the immune action in the Waldeyer's ring and the oronasal mucosa.

5 Such product consists of a physiological solution with a high concentration in a polysaccharide such as glucan.

In particular, two solutions having different concentrations have been specified:

10 - a first physiological solution with a glucan concentration equal to 0.25% for cleaning the nasal fossae and with a preventive hydrating, reepithelializing capability of strengthening the immune action in the Waldeyer's ring and the oronasal
15 mucosa, and

- a physiological solution with a glucan concentration equal to 2% for hydrating and reepithelializing the nasal mucosa, capable of strengthening the immune response in the Waldeyer's
20 ring during the acute phase of the inflammatory, hypertrophic forms of the same.

The inventive concept upon which the invention is based provides the stimulation of the immune system of the tonsillary Waldeyer's ring and the oronasal mucosa
25 by intranasal administration of a polysaccharide capable of activating the tissular macrophages.

It should be remembered that the Waldeyer's ring is the lymphatic tissue located around the inlet of nasopharynx and oropharynx like a ring. It is formed of the pharyngeal, palatal, lingual tonsillae and has the function of blocking microorganisms and exogenic substances at such inlet.

Considering the very high absorption capability of the nasal mucosae and the large amount of immune material in such mucosae and the lymphoid tissue of the Waldeyer's ring annexed thereto, it is believed according to the invention that repeated contacts with a polysaccharide solution having immunotropic activity can prevent the inflammatory or hypertrophic forms thereof or even contribute to their improvement.

It is widely known that the monocytes are mononucleate cells of blood and take part in our defence mechanism. Upon migration to the tissues, they mature, grow, and acquire the capability of phagocytizing. Once activated, tissular macrophages or histiocytes begin to secrete IL-1 (interleukin 1), a proteic messenger that is able to catalyze t-helper lymphocytes by inhibiting a particular receptive site thereof. The active macrophages in the tissues are capable of providing a good defence mechanism as they have a large aspecific phagocytizing ability.

It is also known that tissular macrophages or histiocytes can be activated by the presence of an invader that can also be identified by a polysaccharide chain capable of inhibiting the receptive macrophage site CR3 by the stimulation of

the properdin, a serumal protein able to activate the complement complex, and by concretizing a reaction product composed of B and D factors of such complex.

Among many polysaccharides of biological importance, the attention is drawn to β -(1-3)-glucan which is a polysaccharide molecule extracted from the cellular wall of *Saccharomyces cerevisiae*.

β -(1-3)-glucan has two extremely significant characteristics, namely:

a) the activity of such molecule as biological modifier of the immune response of derma is widely proved. β -(1-3)-glucan has been identified as a strong stimulator of the immunosystem with the capability of activating macrophages, neutrophils and other cells carrying specific β -glucan receptors on their surface. The activation of such cells by glucan stimulates the non-specific defence mechanism of the host. Other polysaccharides such as mannans, galactans, and polymers of glucose chains α (1-4) or β (1-4) haven't got such activity;

b) recent studies have also pointed out the glucan absorption capability of the mucosae by intranasal administration ("Protective Immunity against *Streptococcus mutans* Infection in Mice after Intranasal Immunization with the Glucan-Binding Region of *S. mutans* Glucosyltransferase", Infection and Immunity, Dec. 1999, p. 6543-6549, Vol. 67, No. 12).

According to the invention, therefore, it is provided a contact absorption of a proportion of β -(1-3)-glucan by intranasal administration in order to prevent the

inflammatory or hypertrophic forms of the Waldeyer's ring and/or to contribute to their improvement also by the mechanical action performed by the physiological solution.

5 Therefore, the object of the present invention is a water saline isotonic solution, particularly an isotonic solution of sodium chloride (0.9%) typically used for the parenteral administration of substances in which β -(1-3)-glucan is dissolved.

10 Following the clinical experimentation carried out, two different glucan concentrations capable of providing specific therapeutic responses have been identified, namely:

15 1) a 0.9% Na-solution (physiological solution) with a glucan concentration equal to 0.25% that can be packed in phials of several types and is able to clean the nasal fossae with a preventive capability of strengthening the immune action in the Waldeyer's ring;

20 2) a 0.9% Na-solution (physiological solution) with a glucan concentration equal to 2% packed in phials of several types and able to hydrate the nasal mucosa with a capability of strengthening the immune action in the Waldeyer's ring during the acute phase of the
25 inflammatory forms of the same and its hypertrophic forms.

A very delicate preservative such as sodium benzoate or potassium sorbate may be added to the solutions mentioned above to an adequate extent.

30 As the proximate principle of the disclosed product is

only β -(1-3)-glucan considered as an alimentary component of human diets, the disclosed product may be indifferently used both in adults and children.

5 With regard to this, in order to facilitate the use there are provided confections of single-dose phials with different capacities that can be closed, for example 3.5 or 10 ml.

Claims

1. A product to be administered by nose for preventing inflammatory or hypertrophic forms and strengthening the immune action in the Waldeyer's ring and the oronasal mucosa, characterized in that it consists of a physiological solution with a concentration in a polysaccharide between 0.10 and 4% by weight.

2. The product to be administered by nose of claim 1, characterized in that the polysaccharide is glucan.

3. The product to be administered by nose for cleaning the nasal fossae and with a preventive capability of strengthening the immune action in the Waldeyer's ring and the histiocytes of the oronasal mucosa, characterized in that it consists of a 9% isotonic solution of sodium chloride with a concentration in glucan equal to 0.25% by weight.

4. The product to be administered by nose for hydrating and reepithelializing the nasal mucosa capable of strengthening the immune response in the Waldeyer's ring during the acute phase of the inflammatory, hypertrophic forms of the same, characterized in that it consists of a 0.9% Na-solution (physiological solution) with a concentration in glucan equal to 2% by weight.

5. The product of any preceding claim, characterized

in that glucan is in the form of β -(1-3)-glucan.

6. The product of any preceding claim, characterized in that there is provided a preservative.

5

7. The product of any preceding claim, characterized in that it is packed in single-dose phials.

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 519 009 A (B.A.DONZIS) 21 May 1996 (1996-05-21) claims	1-7
A	FR 2 780 285 A (GOEMAR) 31 December 1999 (1999-12-31) claims	1-7
A	WO 87 01037 A (TULANE EDUCATIONAL FUND) 26 February 1987 (1987-02-26) claims	1-7

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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- *P* document published prior to the international filing date but later than the priority date claimed

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